

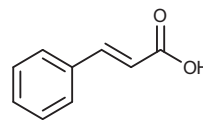
Cimetna kiselina i njeni derivati

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Cimetna kiselina u prirodi

Cimetna kiselina (3-fenilprop-2-enska ili fenilakrilna kiselina, slika 1.) i njeni derivati široko su rašireni u biljnom svijetu. Naziv je dobila po biljnim vrstama iz roda *Cinnamomum* iz porodice Lauraceae u kojima je prisutna u značajnim količinama (1). Najvažniji predstavnik roda je *Cinnamomum verum*, J. Presl. (slika 2.). Nekoliko vrsta iz roda *Cinnamomum* uzgaja se komercijalno za dobivanje začina cimeta (pulvis dobiven iz kore, slika 3.).



Slika 1. Cimetna kiselina

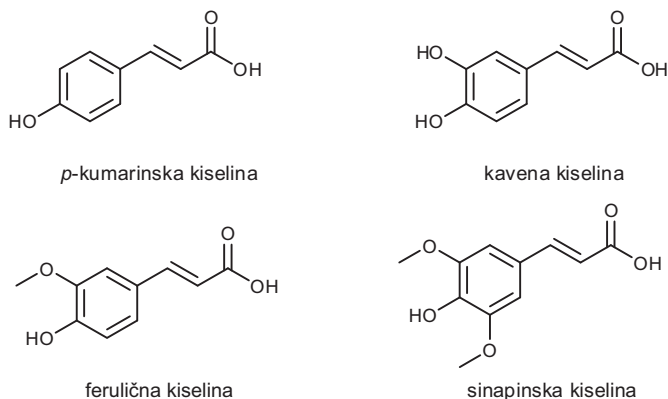
Cimetna kiselina pripada skupini biljnih hormona auksina koji reguliraju rast i diferencijaciju stanica. Biosinteza cimetne kiseline polazi iz aminokiseline L-fenilalanina, a njenom hidroksilacijom nastaju njeni fenolni derivati: *p*-kumarinska, kavena, ferulična i sinapinska kiselina (slika 4.) (4).



Slika 2. *Cinnamomum verum*
(ili *Cinnamomum zeylanicum*, J.
Presl., Lauraceae) (2)



Slika 3. Cimet, začin dobiven od
kore *Cinnamomum* vrsta (3)



Slika 4. Fenolni derivati cimetne kiseline

Cimetna kiselina je ključni intermedijer u biosintezi važnih spojeva kao što su derivati šikimata, fenilpropanoida, stirena, stilbena, kumarina, lignina, izoflavonoida, flavonoida i antocijana, a prisutna je u različitim eteričnim uljima, gumama i balzovima kao slobodna kiselina ili esterificirana (1, 4). Šikiminska kiselina je prekursor u biosintezi mnogih alkaloida, aromatskih aminokiselina i derivata indola. Osim toga, cimetna kiselina je sirovina za sintezu komercijalno važnih spojeva, prije svega njenih estera, koji se koriste u prehrambenoj, farmaceutskoj i kozmetičkoj industriji.

Fizikalno-kemijska svojstva cimetne kiseline

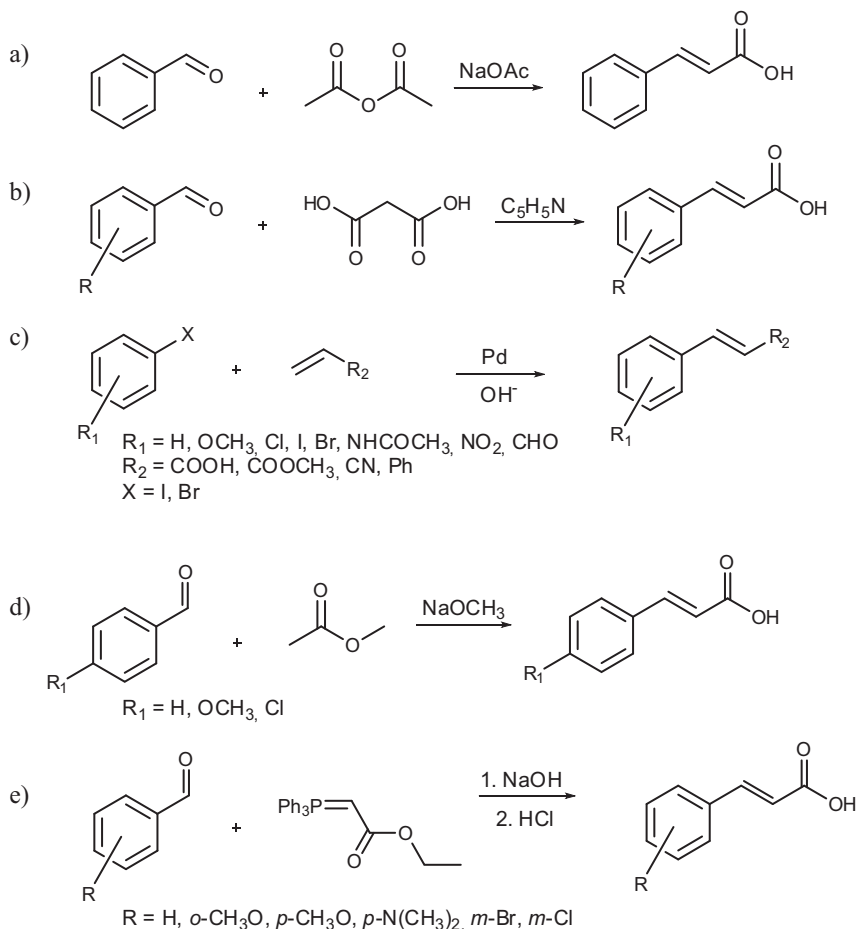
Cimetna kiselina je nezasićena aromatska kiselina. Može postojati kao *cis* i *trans* stereoisomer, a u prirodi je više zastupljen *trans* izomer. Bijela je kristalinična tvar, slabo topljiva u vodi, a dobro topljiva u mnogim organskim otapalima. Miriše po medu. Njena osnovna fizikalno-kemijska svojstva dana su u tablici 1. (5).

Tablica 1. Fizikalno-kemijska svojstva cimetne kiseline

Molekulska formula	$C_9H_8O_2$
Relativna molekulska masa	148,16
Kristalni sustav	monoklinski
Gustoća	$1,2475 \text{ g cm}^{-3}$
Talište	$133 \text{ }^{\circ}\text{C}$
Vrelište	$300 \text{ }^{\circ}\text{C}$
Topljivost u vodi	500 mg L^{-1}
pK_a	4,44

Sinteza cimetne kiseline

Godišnja proizvodnja i potrošnja cimetne kiseline i njenih derivata kreće se od 1–10 tisuća tona (6). U shemi 1. prikazane su najvažnije metode njihove sinteze koje koriste: a) Perkinovu reakciju (6, 7), b) Knoevenagel-Hansovu kondenzaciju (8), c) Heckovu sintezu (9), d) Claisen-Schmidtovu kondenzaciju (10) ili e) Wittigovu reakciju (11).



Shema 1. Najvažnije metode sinteze cimetne kiseline i njenih derivata

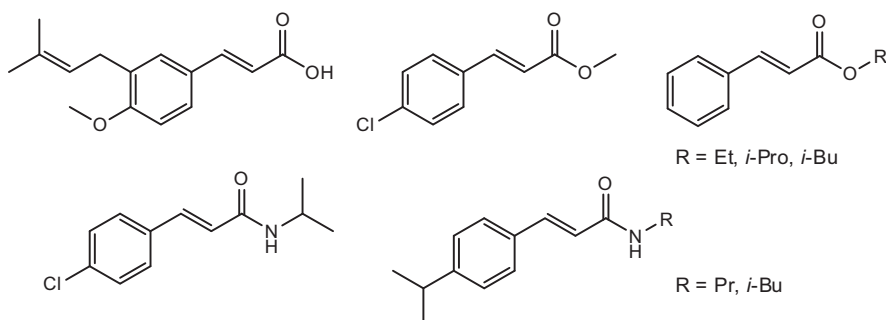
Upotreba cimetne kiseline i njenih derivata

Kao što je već rečeno, derivati cimetne kiseline koriste se u velikim količinama u prehrambenoj, kozmetičkoj i farmaceutskoj industriji. Prvenstveno se koriste kao dodatak pekarskim proizvodima, bezalkoholnim napitcima,

žvakaćim gumama, zubnim pastama i sredstvima za privlačenje insekata. Nadalje, koriste se u proizvodnji sapuna, parfema, šampona, dekorativnih kozmetičkih proizvoda te pripravaka za zaštitu od sunca i vjetra (6). Osim toga, cimetna kiselina važna je sirovina za sintezu L-fenilalanina iz kojeg se proizvodi zaslađivač aspartam.

Biološko djelovanje cimetne kiseline i njenih derivata

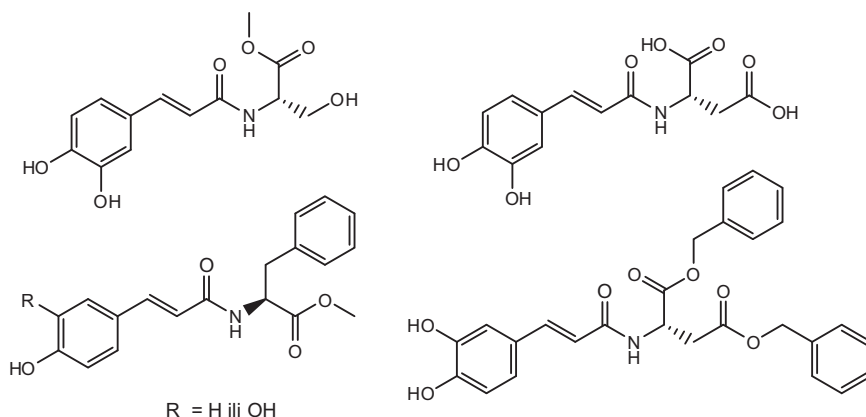
Prirodni i sintetski derivati cimetne kiseline imaju raznoliko farmakološko djelovanje. Postoje bogati literaturni izvori o njihovom antimikrobnom, antituberkulotskom, antioksidativnom, antimikotskom, antidijabetičkom, hepatoprotektivnom, antidepresivnom, hipolipemičkom, antimalarijskom, antivirusnom, anksiolitičkom, protuupalnom i citostatskom djelovanju. Publikacije autora Sharme i Lone i njihovih suradnika daju pregled bioloških djelovanja cimetne kiseline i njenih derivata (6, 12). Metilni ester kavene kiseline ima antimikrobno djelovanje te antitumorsko djelovanje na sarkom (13). Esterski i amidni derivati cimetne kiseline pokazali su značajno antimikrobno (14), a fenilakrilamidni derivati antituberkulotsko djelovanje (15). O antimikrobnom djelovanju derivata cimetne kiseline napisan je i pregledni članak s velikim brojem literaturnih citata (1). Nadalje, objavljeno je antioksidativno djelovanje feniletilnih estera fenolnih derivata cimetne kiseline (16, 17). Spojevi s najjače izraženim djelovanjem na rast i razvoj gljivica prikazani su na slici 5. (18, 19).



Slika 5. Derivati cimetne kiseline s antimikotskim djelovanjem

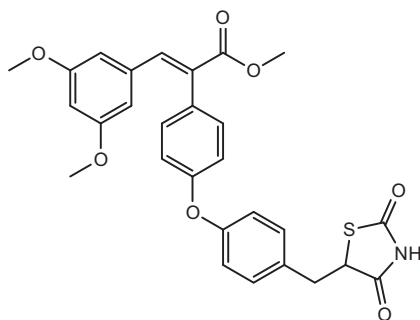
Fenolni derivati cimetne kiseline opisani su kao učinkoviti hepatoprotektivi (20, 21), dok halogenirani derivati djeluju kao depresori središnjeg živčanog sustava (22). Kim i suradnici opisali su hipolipemički učinak derivata kavene kiseline amidirane s aminokiselinama serinom, odnosno asparaginskom kiselinom (23), dok dibenzilester L-asparaginske kiseline amidiran s

kavenom kiselinom i metilni ester L-fenilalanina amidiran s *p*-kumarinskom kiselinom ili kavenom kiselinom inhibiraju pohranu kolesterola i tako djeluju kao antiaterosklerotici (slika 6.) (24, 25).



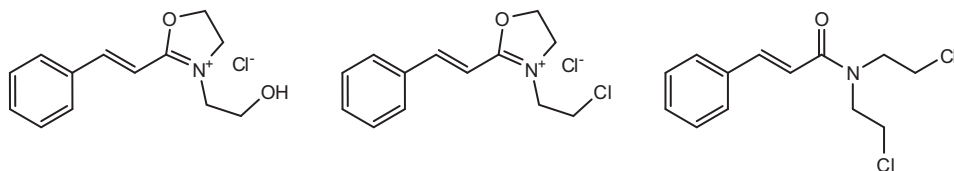
Slika 6. Amidi hidroksicimetne kiseline s aminokiselinama – antihiperlipemici

Derivati ferulične kiseline potiču izlučivanje inzulina (26, 27), a tiazolidinski derivat prikazan na slici 7. vrlo je učinkovit u snižavanju povišene koncentracije glukoze u krvi (28). Nadalje, neki prirodni i sintetski derivati cimetne kiseline potencijalni su protuupalni agensi (29, 30).



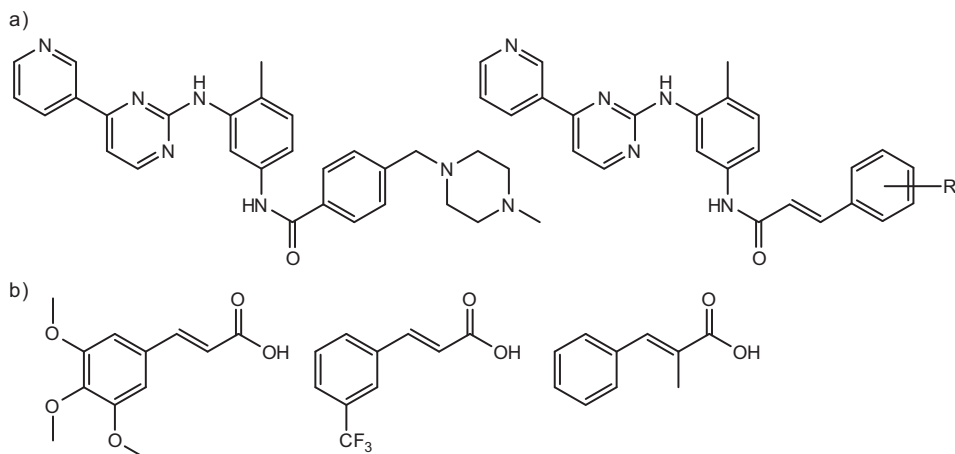
Slika 7. Tiazolidinski derivat cimetne kiseline s antihiperlglikemijskim djelovanjem

U literaturi je opisano i virustatsko djelovanje derivata cimetne kiseline (31). Osim toga, derivati s oksazolinijem i dušikovim iperitom pokazali su citotoksični učinak i mogu poslužiti kao vodeći spojevi za razvoj citostatika (slika 8.) (32).



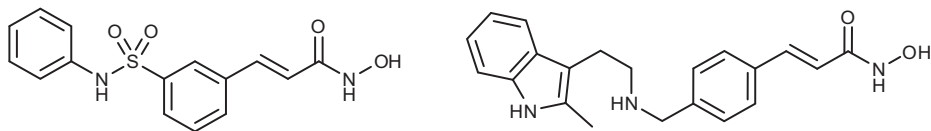
Slika 8. Derivati cimetne kiseline s citotoksičnim učinkom

Sama cimetna kiselina i njeni prirodni fenolni derivati imaju vrlo izraženo antiproliferativno djelovanje. Na slici 9. prikazane su strukture najaktivnijih spojeva koji su sintetizirani po uzoru na njih. Mehanizam antitumorskog djelovanja može uključivati izoprenilaciju proteina, inhibiciju tirozin-kinaze, regulaciju ekspresije metaloproteinaza, indukciju apoptoze, Michaelovu adiciju ili inhibiciju aldo-keto reduktaza (4, 7, 33–35).



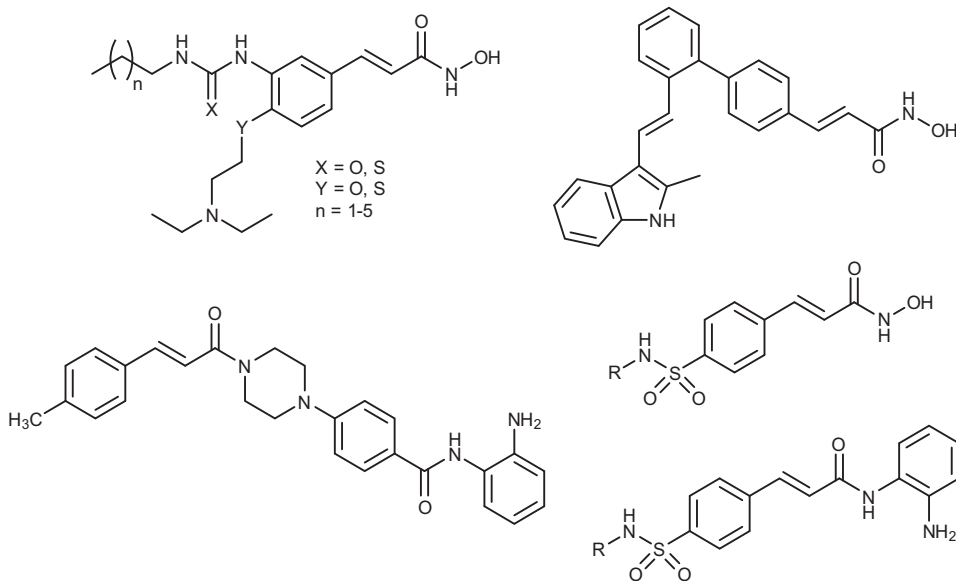
Slika 9. Derivati cimetne kiseline s antitumorskim djelovanjem:
a) inhibitori tirozin-kinaze, b) inhibitori AKR1C3

Derivati cimetne kiseline s hidroksamskom skupinom inhibitori su histonske deacetilaze (HDAC) (4). Najvažniji među njima su belinostat i panobinostat (slika 10.), koji su prije nekoliko godina odobreni za liječenje refraktornog perifernog limfoma T-stanica, odnosno za liječenje multiplog mijeloma (36, 37). Vežu se na aktivno mjesto enzima i keliraju cinkove ione, što dovodi do povećane koncentracije acetiliranih histona i drugih proteina potrebnih za ekspresiju gena nužnih za diferencijaciju stanice (38).



Slika 10. Strukturne formule odobrenih inhibitora HDAC: belinostata i panobinostata

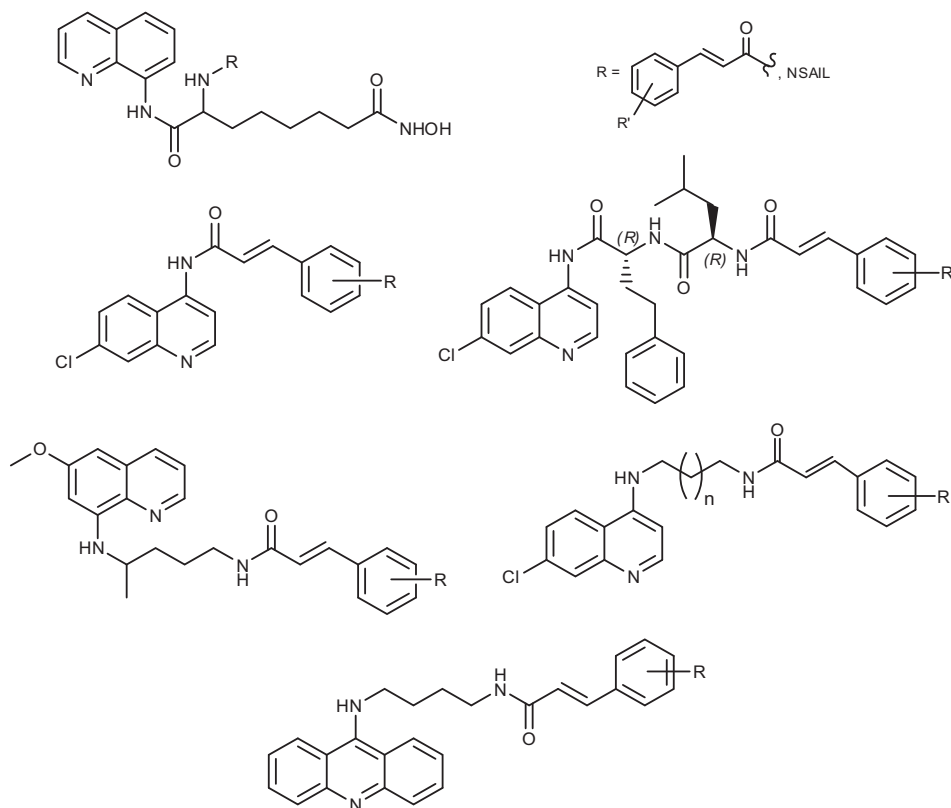
Razvoj novih derivata cimetne kiseline kao potencijalnih inhibitora HDAC vrlo je aktualno područje u farmaceutskoj kemiji. U posljednjih pet godina objavljeno je mnogo radova u kojima je evaluirano citostatsko djelovanje različitih derivata cimetne kiseline kao potencijalnih inhibitora HDAC, a neki od njih su karbamidni i tiokarbamidni derivati cinamohidroksamske kiseline (39), indolil-supstituirane 4-fenilcinamohidroksamske kiseline (40), piperazinski derivati kidamida (41), sulfonamidni derivati cinamohidroksamske kiseline i amidi cimetne kiseline (slika 11.) (42). Mnogi od njih pokazali su slično ili jače antiproliferativno djelovanje od vorinostata, prvog registriranog inhibitora HDAC (43).



Slika 11. Strukturne formule inhibitora HDAC

Inhibitori HDAC-a imaju i antimalarijsko djelovanje (44, 45). Među njima su hibridi aminosuberinske kiseline, 8-aminokinolina i derivata cimetne

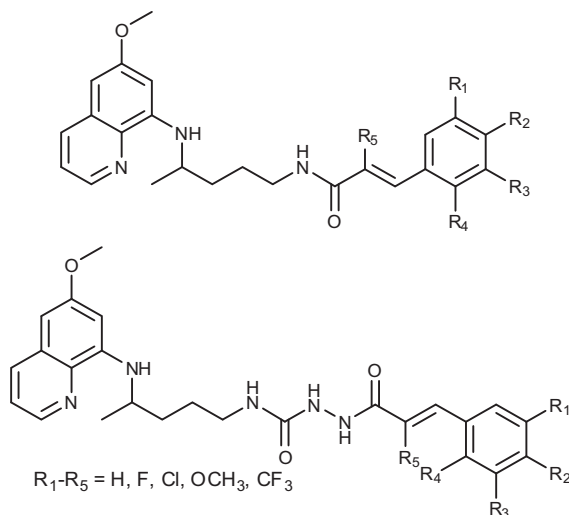
kiseline ili nesteroidnog antiinflatarnog lijeka (45) te hibridi cimetne kiseline i 4-aminokinolina ili primakina povezani izravno, dipeptidnom ili aminoalkilnom poveznicom (slika 12.) (46–49).



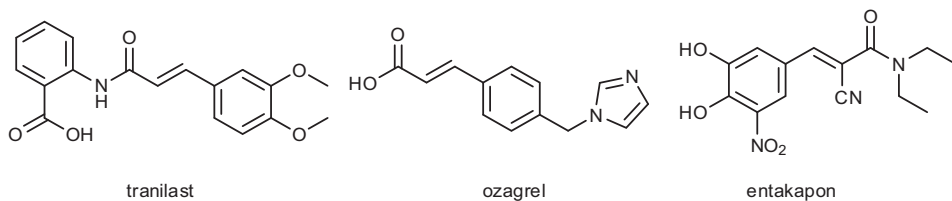
Slika 12. Konjugati aminokinolina i derivata cimetne kiseline s antimalarijskim djelovanjem

Pavić i suradnici objavili su sintezu serije konjugata primakina i cimetne kiseline i njenih derivata povezanih amidnom ili acilsemikarbazidnom skupinom (slika 13.) (50). Spojevi su testirani na antiproliferativno, antivirusno, antioksidativno te antimalarijsko i antituberkulotsko djelovanje (50–53).

Osim u ranije navedenom panobinostatu i belinostatu motiv cimetne kiseline pojavljuje se u nekoliko drugih lijekova iz različitih terapijskih skupina: u tranilastu, ozagrelu te entakaponu (slika 14., tablica 2.).



Slika 13. Konjugati primakina i cimetne kiseline povezani amidnom vezom ili preko acilsemikarbazidne skupine



Slika 14. Registrirani lijekovi koji sadrže motiv cimetne kiseline

Tablica 2. Registrirani lijekovi – derivati cimetne kiseline

Međunarodni nezaštićeni naziv	Farmakološko djelovanje	Zaštićeni naziv	Država u kojoj je registriran
panobinostat	citostatik	Farydak	EU
belinostat	citostatik	Beleodaq	SAD
tranilast	antialergik	Rizaben	Japan, Južna Koreja
ozagrel	antitrombotik	Donenan, Ozagrel, Athrombone	Japan
entakapon	antiparkinsonik	Comtan, Stalevo	SAD, EU, Hrvatska

Cinnamic acid and cinnamic acid derivatives

K. Pavić, B. Zorc

Abstract

Cinnamic acid (3-phenylpropenoic or phenylacrylic acid) and its derivatives occur naturally in a number of plants. They are precursors in the biosynthetic pathways of many alkaloids, aromatic amino acids, phenylpropanoids, styrenes, stilbenes, coumarins, lignins and flavonoids, and are present in various essential oils, gums and balsams. Cinnamic acid derivatives are used in large quantities in the food, cosmetic and pharmaceutical industries. In addition, they possess a variety of pharmacological activities: antimicrobial, anti-tubercular, antioxidative, antimicrobial, antimalarial, antiviral, antidiabetic, hepatoprotective, antidepressant, anxiolytic, hypolipemic, anti-inflammatory and cytostatic activities. Several drugs with cinnamic acid motifs are used in modern therapy (panobinostat, belinostat, cinanserin, tranilast, ozagrel and entacapone).

Literatura – References

1. Guzman JD. Natural cinnamic acids, synthetic derivatives and hybrids with anti-microbial activity. *Molecules*. 2014; 19:292–349.
2. <http://www.absurditii.com.au/cinnamon.html>, pristupljeno 26.4.2018.
3. <http://www.oshims.com/herb-directory/c/cinnamon>, pristupljeno 26.4.2018.
4. De P, Baltas M, Bedos-Belval F. Cinnamic acid derivatives as anticancer agents – a review. *Curr. Med. Chem.* 2011; 18:1672–1703.
5. https://en.wikipedia.org/wiki/Cinnamic_acid, pristupljeno 26.4.2018.
6. Sharma PJ. Cinnamic acid derivatives: A new chapter of various pharmacological activities. *Chem. Pharm. Res.* 2011; 3:403–423.
7. Clayden J, Greeves N, Warren S. *Organic Chemistry*. New York: Oxford University Press Inc., 2012.
8. Kolb KE, Field KW, Schatz PF. A one-step synthesis of cinnamic acids using malonic acid: The Verley-Doebner modification of the Knoevenagel condensation. *J. Chem. Educ.* 1990; 67:A304.
9. Wall VM, Eisenstadt A, Ager DJ, Laneman A. The Heck reaction and cinnamic acid synthesis by heterogeneous catalysis. *Platinum Metals Rev.* 4; 43:138–145.
10. Hatsuda M, Kuroda T, Seki M. An improved synthesis of (E)-cinnamic acid derivatives via the Claisen-Schmidt condensation. *Synth. Commun.* 2003; 33:427–434.
11. Thiemann T, Elshorbagy MW, Salem MHDA, al-Suaibi MAM, al-Hindawi B. One pot reaction of benzaldehydes to cinnamic acids and arylpropionic acids in aqueous medium. 14th International Electronic Conference on Synthetic Organic Chemistry, 2010.

12. Lone R, Shuab R, Koul KK. Role of cinnamate and cinnamate derivatives in pharmacology. *Glob. J. Pharmacol.* 2014; 8:328–335.
13. Nam NH, You YJ, Kim Y, Hong DH, Kim HM, Ahn BZ. Syntheses of certain 3-aryl-2-propenoates and evaluation of their cytotoxicity. *Bioorg. Med. Chem. Lett.* 2001; 11:1173–1176.
14. Narasimhan B, Belsare D, Pharande D, Mourya V, Dhake A. Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations. *Eur. J. Med. Chem.* 2004; 39:827–834.
15. Bairwa R, Kakwani M, Tawari NR, Lalchandani J, Ray MK, Rajan MG, Degani MS. Novel molecular hybrids of cinnamic acids and guanylhya zones as potential antitubercular agents. *Bioorg. Med. Chem.* 2010; 20:1623–1625.
16. Chen JH, Ho CT. Antioxidant activities of caffeic acid and its related hydroxycinnamic acid compounds. *J. Agric. Food Chem.* 1997; 45:2374–2378.
17. Natella F, Nardini M, Di Felice M, Scaccini C. Benzoic and cinnamic acid derivatives as antioxidants: structure-activity relation. *J. Agric. Food Chem.* 1999; 47:1453–1459.
18. Kim JH, Campbell BC, Mahomey NE, Chan KL, Molyneux RJ. Identification of phenolics for control of *Aspergillus flavus* using *Saccharomyces cerevisiae* in a model target-gene bioassay. *J. Agric. Food Chem.* 2004; 52:7814–7821.
19. Tawata S, Taira S, Kobamoto N, Zhu J, Ishihara M, Toyama S. Synthesis and antifungal activity of cinnamic acid esters. *Biosci. Biotechnol. Biochem.* 1996; 60: 909–910.
20. Fernandez-Martinez E, Bobadilla RA, Morales-Rios MS, Muriel P, Perez-Alvarez VM. trans-3-Phenyl-2-propenoic acid (cinnamic acid) derivatives: structure-activity relationship as hepatoprotective agents. *Med. Chem.* 2007; 3:475–479.
21. Saľnikova SI, Dorogovoz SM, Slyshkov VV, Guzhva NN. Hepatoprotective activity of analogs of cinnamic acid. *Farmakol. Toksikol.* 1989; 52:77–80.
22. Na Rao M, Ramanan PN, Kulkarni DR. Central nervous system depressant activity of cinnamic acid derivatives. *Indian J. Pharm. Sci.* 1987; 49:77–79.
23. Kim SJ, S. H. Bok, S. Lee, H. J. Kim, M. K. Lee, Y. B. Park, M. S. Choi, Anticholesterolemic effect of 3,4-di(OH)-phenylpropionic amides in high-cholesterol fed rats, *Toxicol. Appl. Pharmacol.* **208** (1) (2005) 29–36.
24. Park EJ, Lee S, Jeong TS, Bok SH, Lee MK, Park YB, Choi MS. Effect of 3,4-di(OH)-cinnamate synthetic derivative on plasma and hepatic cholesterol level and antioxidant enzyme activities in high cholesterol-fed rats. *J. Biochem. Mol. Toxicol.* 2004; 18:279–287.
25. Lee S, Han JM, Kim H, Kim E, Jeong TS, Lee WS, Cho KH. Synthesis of cinnamic acid derivatives and their inhibitory effects on LDL-oxidation, acyl-CoA: cholesterol acyltransferase-1 and -2 activity, and decrease of HDL-particle size. *Bioorg. Med. Chem. Lett.* 2004; 14:4677–4681.
26. Adisakwattana S, Moonsan P, Yibchok-Anun S. Insulin-releasing properties of a series of cinnamic acid derivatives in vitro and in vivo. *J. Agric. Food Chem.* 2008; 56:7838–7844.

27. Adisakwattana S, Roenqsamran S, Hsu WH, Yibchok-Anun S. Mechanisms of antihyperglycemic effect of p-methoxycinnamic acid in normal and streptozotocin-induced diabetic rats. *Life Sci.* 2005; 78:406–412.
28. Neogi P, Lakner FJ, Medicherla S, Cheng J, Dey D, Gowri M, Nag B, Sharma SD, Pickford LB, Gross C. Synthesis and structure-activity relationship studies of cinnamic acid-based novel thiazolidinedione antihyperglycemic agents. *Bioorg. Med. Chem.* 2003; 11:4059–4067.
29. Takeda Y, Tanigawa N, Sunghwa F, Ninomiya M, Hagiwara M, Matsushita K, Koketsu M. Morroniside cinnamic acid conjugate as an anti-inflammatory agent. *Bioorg. Med. Chem. Lett.* 2010; 20:4855–4857.
30. Kumar S, Arya P, Mukherjee C, Singh BK, Singh N, Parmar VS, Prasad AK, Ghosh B. Novel aromatic ester from *Piper longum* and its analogues inhibit expression of cell adhesion molecules on endothelial cells. *Biochemistry* 2005; 44:15944–15952.
31. Gravina HD, Tafuri NE, Junior AS, Fietto YLR, Oliveira TT, Diaz MAN, Almeida MR. In vitro assessment of the antiviral potential of trans-cinnamic acid, quercetin and morin against equid herpesvirus 1. *Res. Veterinary Sci.* 2010; 91:e158–e162.
32. Hedvati L, Nudelman A, Falb E, Kraiz B, Zhuk R, Sprecher M. Cinnamic acid derived oxazolinium ions as novel cytotoxic agents. *Eur. J. Med. Chem.* 2002; 37:607–616.
33. Liu L, Hudgins R, Shack S, Yin MQ, Samid D. Cinnamic acid: A natural product with potential use in cancer intervention. *Int. J. Cancer* 1995; 62:345–350.
34. Brozic P, Kocbek P, Sova M, Kristl J, Martens S, Adamski J, Gobec S, Lanisnik Rizner T. Flavonoids and cinnamic acid derivatives as inhibitors of 17beta-hydroxysteroid dehydrogenase type 1. *Mol. Cell. Endocrinol.* 2009; 301:229–234.
35. Chang S, Yin SL, Wang J, Jing JK, Dong JH. Design and synthesis of novel 2-phenylaminopyrimidine (PAP) derivatives and their antiproliferative effects in human chronic myeloid leukemia cells. *Molecules* 2009; 14:4166–4179.
36. Lee HZ, Kwitkowski VE, Del Valle PL, Ricci MS, Saber H, Habtemariam BA, Bullock J, Bloomquist E, Li Shen Y, Chen XH, Brown J, Mehrotra N, Dorff S, Charlab R, Kane RC, Kaminskas E, Justice R, Farrell AT, Pazdur R. FDA approval: Belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. *Clin. Cancer Res.* 2015; 21:2666–2670.
37. Laubach JP, Moreau P, San-Miguel JF, Richardson PG. Panobinostat for the treatment of multiple myeloma. *Clin. Cancer Res.* 2015; 21:4767–4773.
38. Richon VM. Cancer biology: Mechanism of antitumour action of vorinostat (suberoylanilide hydroxamic acid), a novel histone deacetylase inhibitor. *Brit. J. Cancer.* 2006; 95:S2–S6.
39. Ning C, Bi Y, He Y, Huang WY, Liu L, Li Y, Zhang S, Liu X, Yu N. Design, synthesis and biological evaluation of di-substituted cinnamic hydroxamic acids bearing urea/thiourea unit as potent histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* 2013; 23:6432–6435.

40. Cincinelli R, Zwick V, Musso L, Zuco V, de Cesare M, Zunino F, Simoes-Pires C, Nurisso C, Giannini G, Cuendet M. Biphenyl-4-yl-acrylohydroxamic acids: Identification of a novel indolyl-substituted HDAC inhibitor with antitumor activity. *Eur. J. Med. Chem.* 2016; 112:99–105.
41. Zhang Q, Lu B, Li J. Design, synthesis and biological evaluation of 4-piperazinyl-containing chidamide derivatives as HDACs inhibitors. *Bioorg. Med. Chem. Lett.* 2017; 27:3162–3166.
42. Wang L, Bao X, Yang J, Li H, Zhou Q, Jiang X, Li M, Liu X, Yuan X, Sun Y, Chen J, Zhang J, Chen G, Wu C. Novel cinnamohydroxamic acid derivatives as HDAC inhibitors with anticancer activity in vitro and in vivo. *Chem. Biol. Inter.* 2016; 249:64–70.
43. <http://reference.medscape.com/drug/zolinza-vorinostat-342102>, pristupljeno 31.8. 2017.
44. Mukherjee P, Pradhan A, Shah F, Tekwani BL, Avery MA. Structural insights into the *Plasmodium falciparum* histone deacetylase 1 (PfHDAC-1): A novel target for the development of antimalarial therapy. *Bioorg. Med. Chem.* 2008; 16:5254–5265.
45. Wheatley NC, Andrews KT, Tran TL, Lucke AJ, Reid RC, Fairlie DP. Antimalarial histone deacetylase inhibitors containing cinnamate or NSAID components. *Bioorg. Med. Chem. Lett.* 2010; 20:7080–7084.
46. Pérez BC, Teixeira C, Albuquerque IS, Gut J, Rosenthal PJ, Prudencio M, Gomes P. PRIMACINS, *N*-cinnamoyl-primaquine conjugates, with improved liver-stage antimalarial activity. *Med. Chem. Commun.* 2012; 3:1170–1172.
47. Pérez BC, Teixeira C, Gomes AS, Albuquerque IS, Gut J, Rosenthal PJ, Prudêncio M, Gomes P. In vitro efficiency of 9-(*N*-cinnamoylbutyl)aminoacridines against blood- and liver-stage malaria parasites. *Bioorg. Med. Chem. Lett.* 2013; 23:610–613.
48. Pérez BC, Teixeira C, Figueiras M, Gut J, Rosenthal PJ, Gomes JRB, Gomes P. Novel cinnamic acid/4-aminoquinoline conjugates bearing non-proteinogenic amino acids: Towards the development of potential dual action antimalarials. *Eur. J. Med. Chem.* 2012; 54:887–899.
49. Pérez BC, Teixeira C, Albuquerque IS, Gut J, Rosenthal PJ, Gomes JRB, Prudencio M, Gomes P. *N*-Cinnamoylated chloroquine analogues as dual-stage antimalarial leads. *J. Med. Chem.* 2013; 56:556–567.
50. Pavić K, Perković I, Gilja P, Kozlina F, Ester K, Kralj M, Schols D, Hadjipavlou-Litina D, Pontiki E, Zorc B. Design, synthesis and biological evaluation of novel primaquine-cinnamic acid conjugates of amide and acylsemicarbazide type. *Molecules* 2016; 21:1629–1653.
51. Pavić K, Perković I, Pospíšilová Š, Machado M, Fontinha D, Prudêncio M, Jampilek J, Coffey A, Endersen L, Rimac H, Zorc B. Primaquine hybrids as promising antimycobacterial and antimalarial agents. *Eur. J. Med. Chem.* 2018; 143:769–779.
52. Levatić J, Pavić K, Perković I, Uzelac L, Ester K, Kralj M, Kaiser M, Rottmann M, Supek F, Zorc B. Machine learning prioritizes synthesis of primaquine

- ureidoamides with high antimalarial activity and attenuated cytotoxicity. Eur. J. Med. Chem. 2018; 146:651–667.
- 53.** Mabeta P, Pavić K, Zorc B. Insights into mechanism of antiproliferative effect of primaquine-cinnamic acid conjugates on MCF-7. Acta Pharm. 2018; 68 (u tisku) <https://doi.org/10.2478-2018-0021>.

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